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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/800,629	03/07/2001	Nicholas M. Dean	ISPH-0537	8249

7590 08/14/2002

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EXAMINER
GIBBS, TERRA C

ART UNIT	PAPER NUMBER
1635	11

DATE MAILED: 08/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/800,629	DEAN ET AL.	
	Examiner	Art Unit	
	Terra Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-72 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-72 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-72 are pending in the instant application.

Specification

The references to the American Type Culture Collection found in the instant specification at page 48, 66-67, 69 and 73 must include a *current* and *complete* address, including street address.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of modulating the expression of human and murine interleukin-5 and interleukin-5 receptor α gene in cells *in vitro* (e.g. cells in culture) does not reasonably provide for a method of modulating the expression of an interleukin-5 and interleukin-5 receptor α gene in cells *in vivo* (e.g. whole animal). Nor does the specification provide enablement for a diagnostic kit for detecting the expression level of interleukin-5 receptor α. The specification does not enable any person or skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 49-72 are broadly drawn to oligonucleotides comprising 8 to 30 nucleotides wherein said nucleotide modulates the expression of mammalian interleukin-5 and interleukin-5 receptor α; a method of modulating the expression of mammalian interleukin-5 and interleukin-5 receptor α in mammalian cells or tissues; a method of treating a mammalian having a disease or condition associated with interleukin-5 and interleukin-5 receptor α; and a diagnostic kit for detecting the expression level of interleukin-5 receptor α.

The specification as filed shows *in vitro* modulation of human and murine interleukin-5 (IL-5) and interleukin-5 receptor α (IL-5 Rc α) following antisense treatment in EL-4, CEM, HSB-2 and TF-1 cells. The specification as filed further shows antisense inhibitory effect of IL-5 on eosinophilia in an ovalbumin murine lung model. The instant specification also shows the induction of apoptosis in TF-1 cells treated with IL5 Rc α and inhibition of agonist-induced proliferation in TF-1 cells.

The instant specification fails to teach the core or essential elements possessed by the claimed methods of modulating the expression of mammalian interleukin-5 and interleukin-5 receptor α in mammalian cells or tissues (*in vivo*) such that modulation would correlate to treating a mammalian having a disease or condition associated with interleukin-5 and interleukin-5 receptor α. The specification as filed does not provide adequate guidance of examples that would show by correlation the practice of the instant invention without the need for undue trail and error experimentation. The specification does not provide a meaningful nexus between modulating the expression of interleukin-5 and interleukin-5 receptor α in mammalian cells or tissues *in vitro* to modulating the expression of interleukin-5 and interleukin-5 receptor α in mammalian cells or tissues *in vivo.* It is unpredictable as to whether *in vitro*

modulation of interleukin-5 and interleukin-5 receptor α correlates with modulation of interleukin-5 and interleukin-5 receptor α *in vivo*.

The specification as filed shows antisense oligonucleotides as a mode for modulation of interleukin-5 and interleukin-5 receptor α *in vitro* and *in vivo*. Regarding the level of predictability or unpredictability associated with the antisense therapeutic art, Crooke (1998: Stanley T. Crooke, Basic Principles of Anitsense Therapeutics, Springer-Verlag, NY, p. 3. ,1998), states "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate and, in fact, there are now several lines of evidence in animals and man [that] demonstrate that, even after careful consideration of all *in vitro* uptake data, one cannot predict *in vivo* pharmacokinetics of the compounds based on *in vitro* studies."

It is clear from Crooke that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

Branch (TIBS Vol 23, February 1998) further adds to the lack of enablement for the current invention. For example, Branch addresses the unpredictability and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest."; "However, their unpredictability

confounds research application of nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,..."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*."

It would appear that in view of the above, one of ordinary skill in the art would have to engage in undue trial and error experimentation to practice the instant invention. In view of the

unpredictability of the art, the quantity of experimentation required would include the specific doses utilized, the exact routes of administration, the regimen employed, the intracellular target, variability in contact time and therapeutic efficacy that specifically modulate the expression of interleukin-5 and interleukin-5 receptor α... in addition to overcoming the obstacles to routine antisense therapies as exemplified in the references discussed above. Therefore, undue experimentation would be required of one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 3, 7, 8, 49 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Weltman et al. [U.S. Patent No. 6,048,726].

Claims 1, 2, 3, 7, 8, 49 and 50 are drawn to antisense oligonucleotides comprising 8 to 30 nucleotides in length which modulate the expression of mammalian interleukin-5; wherein the antisense is an antisense oligonucleotide; wherein the antisense has at least one modified internucleoside linkage such as a phosphatorothioate linkage; wherein mammalian interleukin-5 is modulated in cells or tissues.

Weltman et al. disclose an oligonucleotide consisting of 16 nucleotides in length wherein said nucleotide is an antisense oligonucleotide which modulates the expression of mammalian interleukin-5 (see claims 2 and 6) as in claims 1, 2 and 3. Weltman et al. further disclose a method of inhibition interleukin-5 signal transduction *in vitro* by contacting a cell with an antisense nucleic acid of interleukin-5 and inhibiting interleukin-5 expression (see Figures1 and 2 and claim 6) as in claims 49 and 50. Weltman et al. further disclose modified oligonucleotides with at least one phosphorothioate internucleotide linkage (see column 1, lines 36-38) as in claims 7 and 8.

Claims 5 and 51 are rejected under rejected under 35 U.S.C. 102(b) as being anticipated by Nyce et al. [WO 96/40162].

Claims 5 and 51 are drawn to antisense oligonucleotides comprising 8 to 30 nucleotides in length which modulate the expression of mammalian interleukin-5 receptor α; wherein mammalian interleukin-5 receptor α is modulated in cells or tissues.

Nyce et al. disclose oligonucleotides between 8 and 30 nucleobases targeted to human interleukin-5 receptor α (see page 31, lines 1-24 and claim 5) as in claim 5. Nyce et al. futher disclose a method of inhibition of interleukin-5 receptor α by contacting a cell or tissues with an antisense nucleic acid of interleukin-5 receptor α and inhibiting interleukin-5 receptor α expression (see page 4, lines 14-19 and claims 1 and 5) as in claim 51.

Claims 13 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Bennett et al. [U.S. Patent No. 6,210,892].

Claims 13 and 40 are drawn to an antisense compound of at least an 8-nucleobase portion of SEQ ID No: 209.

Bennet et al. disclose a 15-nucleobase portion of SEQ ID NO: 209 (see Bennett et al. SEQ ID No: 2).

Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Dolganov et al. [U.S. Patent No. 5,821,091].

Claim 4 is drawn to an antisense compound up to 30 nucleobases in length comprising at least an 8-nucleobase portion of SEQ ID NOs: 52, 53 or 62 which inhibits the expression of mammalian interleukin-5.

Dolganov et al. disclose a 24 nucleobase sequence having 100% homology to bases 1-20 of instant SEQ ID NO: 52 (see Dolganov et al. SEQ ID No: 14).

Claim Rejections – 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 2, 7-23, 49, 3 and 4, and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weltman et al. [U.S. Patent No. 6,048,726], and further in view of Dolganov et al. [U.S. Patent No. 5,821,091], Sahasrabudhe et al. (Journal of Biomolecular Structure and Dynamics, 1996 Vol. 13:585-590), Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

Claims 1 and 2, 7-23, 49 are generically drawn to antisense oligonucleotides of 8 to 30 nucleobases in length which modulate interleukin 5- signal transduction; wherein: the antisense oligonucleotide comprises at least one modified internucleoside linkage; the modified internucleoside linkage of the antisense oligonucleotide is a phosphorothioate linkage; the modified internucleoside linkage of the antisense is a peptide nucleic acid which comprises at least one basic amino acid conjugated to at least one end of the antisense compound which is less than 20 nucleobases in length; the basic amino acid is lysine or arginine nucleobase; at least one of the nucleotides has a modified sugar moiety; the sugar moiety of that antisense is a 2'-O-methoxyethyl sugar moiety; the antisense comprises at least one modified nucleobase; wherein the modified nucleobase is 5-methylcytosine; each 2'-O-methoxyethyl modified cytosine nucleobase of the antisense is as 5-methylcytosinep; the antisense is a chimeric; a pharmaceutical composition comprising a colloidal dispersion system and a pharmaceutically acceptable carrier or diluent. Claims 3 and 4 are drawn to the antisense of claim 1 which is targeted to a nucleic acid molecule encoding mammalian interleukin-5; wherein the antisense is up to 30 nucleobases in length comprising at least an 8-nucleobase portion of SEQ ID NO: 52, 53 or 62. Claim 50 is

drawn to a method of modulating the expression of interleukin-5 in cells or tissues with an interleukin-5 antisense.

Weltman et al. teach an oligonucleotide consisting of 16 nucleotides in length wherein said nucleotide is an antisense oligonucleotide which modulates the expression of mammalian interleukin-5 (see claims 2 and 6). Weltman et al. further teach a method of inhibition of interleukin-5 expression *in vitro* by contacting a cell with an antisense nucleic acid of interleukin-5 and inhibiting interleukin-5 expression (see claim 6). Weltman et al. further teach modified oligonucleotides with at least one phosphorothioate internucleotide linkage (see column 1, lines 36-38).

Dolganov et al. disclose a 24 nucleobase sequence having 100% homology to bases 1-20 of instant SEQ ID NO: 52 (see Dolganov et al. SEQ ID No: 14).

Weltman et al. and Dolganov et al. not teach the antisense oligonucleotide of claim 1 wherein: the modified internucleoside linkage of the antisense is a peptide nucleic acid which comprises at least one basic amino acid conjugated to at least one end of the antisense compound which is less than 20 nucleobases in length; the basic amino acid is lysine or arginine nucleobase; at least one of the nucleotides has a modified sugar moiety; the sugar moiety of that antisense is a 2'-O-methoxyethyl sugar moiety; the antisense comprises at least one modified nucleobase; wherein the modified nucleobase is 5-methylcytosine; each 2'-O-methoxyethyl modified cytosine nucleobase of the antisense is as 5-methylcytosinep; the antisense is a chimeric; a pharmaceutical composition comprising a colloidal dispersion system and a pharmaceutically acceptable carrier or diluent.

Sahasrabudhe et al. and Baracchini teach the limitation of the antisense oligonucleotide of claim 1.

Sahasrabudhe et al. teach oligodeoxynucleotide-peptide conjugate complexed to an RNA hairpin loop. Sahasrabudhe et al. also teach the peptide portion of the oligodeoxynucleotide-peptide conjugate was covalently attached to aspartic acid (see Abstract). Sahasrabudhe et al. further teach lysine was chosen because electrostatic attraction between the positively charged side chains of the peptide and the phosphodiester backbone of the RNA hairpin stem would favor complex formation (see page 589, first paragraph).

Baracchini et al. teach at least one of the nucleotides has a modified sugar moiety, (see page column, lines 58-59). Baracchini et al. teach the sugar moiety of that antisense is a 2'-O-methoxyethyl sugar moiety (see Tale I). Baracchini et al. further teach oligonucleotides with one modified nucleobase (see column 7, lines 15-20). Baracchini et al. further teach oligonucleotides comprising 5-methylcytosine (see column 7, line 23). Baracchini et al. further teach chimeric oligonucleotides (see column 8, lines 10-12). Baracchini et al. further teach oligonucleotides may be formulated in a pharmaceutical composition, which may include carriers, thickeners, diluents, buffers, liposomes or lipid formulations (see column 4, lines 26-31). Baracchini et al. assert that oligonucleotides composed of modified nucleobases are preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases (see column 6, lines 24-34).

Baracchini et al. do not teach a colloidal dispersion system.

Fritz et al. teach a suitable model drug delivery system for oligonucleotides. Fritz et al. further teach in that in combination with steric stabilizers, oligonucleotides exhibit high colloidal

stability with low toxic side effects as is required for biological experiments in cell culture and *in vivo* (see page 297, last paragraph).

It would have been obvious to combine the teachings of Weltman et al., Dolganov et al., Baracchini et al., and Fritz et al. to make the instant invention. One of ordinary skill in the art would have been motivated to make antisense oligonucleotides that modulate the expression of interleukin-5 since Weltman et al. and Dolganov et al. taught the use of antisense oligonucleotides as inhibitors of expression of interleukin-5 and in various cells and tissues. One of ordinary skill in the art would have been motivated to modify oligonucleotides which modulate the expression of interleukin-5 and had a reasonable expectation of success the prior art taught the use of such modified oligonucleotides are preferred over native forms because of desirable properties such as desired complex formation, enhanced cellular uptake, enhanced affinity for nucleic acid targets, increased stability in the presence of nucleases and low toxicity (Sahasrabudhe et al., Baracchini et al. and Fritz et al.).

Claims 1 and 2, 7-23, 49, 5 and 6 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce et al. [WO 96/40162], Bennett et al. [U.S. Patent No. 6,210,892], Sahasrabudhe et al. (Journal of Biomolecular Structure and Dynamics, 1996 Vol. 13:585-590), Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

The limitations of generic claims Claims 1 and 2, 7-23, 49 are recited above. Claim 5 and 6 are drawn to the antisense of claim 1 which is targeted to a nucleic acid molecule encoding mammalian interleukin-5 receptor α; wherein the antisense is up to 30 nucleobases in length

comprising at least an 8-nucleobase portion of SEQ ID NO: 162, 166, 167, 169, 170, 171 or 172. Claim 51 is drawn to a method of modulating the expression of interleukin-5 receptor α in cells or tissues with an interleukin-5 receptor α antisense.

Nyce et al. teach oligonucleotides between 8 and 30 nucleobases targeted to human interleukin-5 receptor α (see page 31, lines 1-24 and claim 5). Nyce et al. futher teach a method of inhibition of interleukin-5 receptor α by contacting a cell or tissues with an antisense nucleic acid of interleukin-5 receptor α and inhibiting interleukin-5 receptor α expression (see page 4, lines 14-19 and claims 1 and 5).

Bennet et al. disclose a 15-nucleobase portion of SEQ ID NO: 209 (see Bennett et al. SEQ ID No: 2).

Nyce et al. and Bennet et al. do teach the antisense oligonucleotide of claim 1 wherein: the modified internucleoside linkage of the antisense is a peptide nucleic acid which comprises at least one basic amino acid conjugated to at least one end of the antisense compound which is less than 20 nucleobases in length; the basic amino acid is lysine or arginine nucleobase; at least one of the nucleotides has a modified sugar moiety; the sugar moiety of that antisense is a 2'-O-methoxyethyl sugar moiety; the antisense comprises at least one modified nucleobase; wherein the modified nucleobase is 5-methylcytosine; each 2'-O-methoxyethyl modified cytosine nucleobase of the antisense is as 5-methylcytosinep; the antisense is a chimeric; a pharmaceutical composition comprising a colloidal dispersion system and a pharmaceutically acceptable carrier or diluent.

Sahasrabudhe et al. and Baracchini teach the limitation of the antisense oligonucleotide of claim 1.

Sahasrabudhe et al. teach oligodeoxynucleotide-peptide conjugate complexed to an RNA hairpin loop. Sahasrabudhe et al. also teach the peptide portion of the oligodeoxynucleotide-peptide conjugate was covalently attached to aspartic acid (see Abstract). Sahasrabudhe et al. further teach lysine was chosen because electrostatic attraction between the positively charged side chains of the peptide and the phosphodiester backbone of the RNA hairpin stem would favor complex formation (see page 589, first paragraph).

Baracchini et al. teach at least one of the nucleotides has a modified sugar moiety, (see page column, lines 58-59). Baracchini et al. teach the sugar moiety of that antisense is a 2'-O-methoxyethyl sugar moiety (see Tale I). Baracchini et al. further teach oligonucleotides with one modified nucleobase (see column 7, lines 15-20). Baracchini et al. further teach oligonucleotides comprising 5-methylcytosine (see column 7, line 23). Baracchini et al. further teach chimeric oligonucleotides (see column 8, lines 10-12). Baracchini et al. further teach oligonucleotides may be formulated in a pharmaceutical composition, which may include carriers, thickeners, diluents, buffers, liposomes or lipid formulations (see column 4, lines 26-31). Baracchini et al. assert that oligonucleotides composed of modified nucleobases are preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid targets and increased stability in the presence of nucleases (see column 6, lines 24-34).

Baracchini et al. do not teach a colloidal dispersion system.

Fritz et al. teach a suitable model drug delivery system for oligonucleotides. Fritz et al. further teach in that in combination with steric stabilizers, oligonucleotides exhibit high colloidal stability with low toxic side effects as is required for biological experiments in cell culture and *in vivo* (see page 297, last paragraph).

It would have been obvious to combine the teachings of Nyce et al., Bennet et al., Baracchini et al., and Fritz et al. to make the instant invention. One of ordinary skill in the art would have been motivated to make antisense oligonucleotides that modulate the expression of interleukin-5 receptor α since Nyce et al. and Bennet et al. taught the use of antisense oligonucleotides as inhibitors of expression of interleukin-5 Rc α in various cells and tissues. One of ordinary skill in the art would have been motivated to modify oligonucleotides which modulate the expression of interleukin-5 Rc α and had a reasonable expectation of success the prior art taught the use of such modified oligonucleotides are preferred over native forms because of desirable properties such as desired complex formation, enhanced cellular uptake, enhanced affinity for nucleic acid targets, increased stability in the presence of nucleases and low toxicity (Sahasrabudhe et al., Baracchini et al. and Fritz et al.).

The invention as a whole would therefore have been obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
August 12, 2002

SEAN McGARRY
PRIMARY EXAMINER